TYPE-I-INTERFERON ACTIVATES CROSS-DRESSED CD11b⁺CONVENTIONAL DENDRITIC CELLS TO ENHANCE ANTI-TUMOR IMMUNITY

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Background Conventional dendritic cells (cDC) are critical mediators of protective anti-tumor CD8⁺ T-cell responses.¹ Batf3-driven DC1 are the predominant cDC subset driving anti-tumor immunity due to their specialized ability to cross-present antigens for T-cell activation.^{2–4} However, the contribution of other tumor-infiltrating DC subsets such as CD11b⁺ DC2 to anti-tumor immunity remains poorly characterized. Recent studies suggest that under inflammation, DC subsets can exist in various functional states with differential impacts on their stimulatory potential.^{5–7} In this study, we sought to dissect the contributions of distinct DC states during a productive or dysfunctional anti-tumor immune response. A nuanced understanding of DC activation states in tumors and the signals that drive them carries therapeutic potential to modulate anti-tumor immunity and enhance immunotherapy responses.

Methods We compared the DC infiltrate of a regressing tumor and a progressing tumor to study DC states. Flow immunophenotyping and RNA-sequencing was performed to profile the intratumoral DC compartment. Sorted DC subsets were co-cultured with T-cells *ex vivo* to evaluate their stimulatory capacity. Cross-dressing (*in vivo/ex vivo*) was assayed by staining for transfer of tumor-derived H-2^b MHC complexes to MHC-mismatched or β 2M-deficient DC.

Results Anti-tumor CD8⁺ T-cell responses in Batf3^{-/-} mice lacking DC1 were maintained in regressor tumors but not progressor tumors, suggesting DC1-independent anti-tumor immunity. Functional assays and RNA-sequencing of the intratumoral DC compartment of regressor tumors revealed a Zbtb46-dependent CD11b⁺ cDC activation state expressing an interferon-stimulated gene signature (ISG⁺ DC) that was critical for driving optimal anti-tumor CD8⁺ T-cell responses. Sorted ISG⁺ DC could activate CD8⁺ T-cells similar to DC1. Unlike cross-presenting DC1, however, ISG⁺ DC acquired antigens by cross-dressing with tumor-derived peptide-MHC, thereby bypassing the requirement for cross-presentation to initiate CD8⁺ T-cell-immunity. Interestingly, ISG⁺ DC were enriched in regressor tumors compared to progressor tumors, and this was attributable to constitutive tumor cell-intrinsic type-I-interferon (IFN-I) production in regressor tumors. Ablation of tumor cell-derived IFN-I in regressor tumors led to complete loss of anti-tumor T-cell responses in Batf3^{-/-} mice. Conversely, addition of IFN β to progressor tumors induced ISG⁺ DC and rescued anti-tumor T-cell responses in Batf3^{-/-} mice.

Conclusions We identified a novel IFN-I-induced activation state of CD11b⁺ cDC, called ISG⁺ DC, that was capable of driving anti-tumor CD8⁺ T cell immunity by cross-dressing with tumor-derived pMHC complexes in the absence of DC1. Engaging additional functional states of DC, such as ISG⁺ DC, will strengthen anti-tumor immunity and may improve immunotherapy responses.

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